outgrowth. Accordingly, the Examiner asserts that one skilled in the art would expect a Rho kinase inhibitor to be successful in treating conditions from injury to the corneal nerve (as in Hellberg), because McKerracher indicates that Rho kinase inhibitors are effective to stimulate neurite outgrowth, and Hellberg teaches that compounds which promote neurite outgrowth are successful in the method. Further, the Examiner stated that Hara teaches fasudil hydrochloride as a known Rho kinase inhibitor.

Applicants argued that neither McKerracher nor Hara refer to corneal nerve injury, and that Applicants discovered ***for the first time*** that the corneal nerve contains a site of action of Rho kinase, which could not be predicted based upon the common knowledge in the art at the time the application was filed.

The Examiner pointed to the teachings within McKerracher regarding treatment of retinal neurons and the optic nerve, as well as the teachings on page 15, lines 10-15 regarding Rho kinase inhibitors' usefulness in treating conditions and ailments of the PNS and the CNS where treatment to increase neurite extension, growth, or regeneration is desired. In view of these teachings, the Examiner indicated that one of ordinary skill in the art would expect an active agent which is taught for treating any part of the nervous system to be successful in treating the corneal nerve.

The Examiner provided the following helpful recommendation, which she indicated would assist in overcoming the rejection. Examiner Huang suggested providing evidence regarding why one skilled in the art would not expect an active agent which treats retinal neuron conditions, optic nerve conditions, and PNS and CNS conditions to be successful in treating a *corneal nerve condition*. In other words, the Examiner suggested that Applicants explain why the method of promoting neuritogenesis of corneal nerves with a Rho kinase inhibitor is unexpected.

Applicants appreciate the Examiner's helpful suggestions, and provide the recommended evidence in a Declaration under 37 CFR 1.132, submitted herewith.

Rejection Under 35 U.S.C. § 103(a)

Claim 13 is rejected under 35 U.S.C. § 103(a) as being unpatentable over Hellberg et al. (WO 03/020281) in view of McKerracher et al. (WO 99/23113) and Hara et al. (Protein kinase inhibition by fasudil hydrochloride promotes neurological recovery after spinal cord injury in rats). This rejection is respectfully traversed.

The Examiner's position, as clarified in the personal interview with Applicants' representative on April 19, 2011, is discussed above. As argued during the interview, none of the references relied upon by the Examiner teach or suggest that the corneal nerve contains a site of action of Rho kinase. Specifically, the Hellberg reference teaches the use of other compounds for promotion of neuron regeneration of neurite outgrowth for treatment of conditions resulting from corneal nerve injury; McKerracher teaches the use of Rho kinase inhibitors for stimulating neurite outgrowth; and Hara teaches fasudil hydrochloride. However, neither McKerracher nor Hara even mention *corneal nerve injury*.

The Examiner asserts that McKerracher teaches treatment of retinal neurons and the optic nerve, and discusses Rho kinase inhibitors' usefulness in treating conditions and ailments of the PNS and CNS where treatment to increase neurite extension, growth, or regeneration is desired. The Examiner acknowledges that McKerracher and Hara fail to teach even mention corneal nerve injury. However, the Examiner bases her rejection on her understanding that an active agent which is taught for treatment any part of the nervous system will be successful in treating the corneal nerve. Applicants respectfully disagree with this assertion.

In accordance with the Examiner's helpful suggestion, Applicants provide evidence (in the form of a Declaration under 37 CFR 1.132) which demonstrates the following:

(1) That the optic (retinal) nerve and the trigeminal (ophthalmic=corneal) nerve are entirely different from each other in their functions and structures;

(2) That the corneal nerve and the optic (retinal) nerve are also different from each other in diseases/conditions caused by their injuries; and therefore,

(3) That one skilled in the art would not expect an active agent that treats optic (retinal) nerve conditions to be successful in treating trigeminal (corneal) nerve conditions.

Careful consideration of the enclosed Declaration is respectfully requested.

It is clear from the evidence provided that merely because Rho kinase inhibitors are taught for treatment of retinal neurons and the optic nerve, it would not have been obvious to one of ordinary skill in the art to employ Rho kinase inhibitors for promoting neuritogenesis of corneal nerves that are damaged, cut or defective by a corneal surgery or corneal disease, as required by Applicants' claims.

The Declaration also describes:

(4) That McKerracher does not teach Rho kinase inhibitors, but rather, Rho antagonists such as C3 enzyme and a dominant negative Rho;

(5) That Hara teaches fasudil as not only Rho kinase inhibitor, but also an inhibitor of other various protein kinases, including protein kinase C (PKC) and myosin light chain kinase (MLCK); and

(6) That Rho kinase inhibitors are not neurotrophic factor stimulators.

Thus, based on the teachings of the cited references, one of ordinary skill in the art would not even expect that Rho kinase inhibitors treat retinal and spinal cord nerve conditions, since McKerracher and Hara do not teach *Rho kinase inhibitors*, as required by Applicants' claims. Rather, McKerracher teaches Rho agonists, which block other signal pathways via other Rho effectors in addition to the ROCK signal pathway. Thus, one of ordinary skill in the art would not have been motivated to replace the Rho antagonists of McKerracher with the specific Rho kinase inhibitors required by Applicants' claim 13 to treat retinal and spinal cord nerve injuries. Further, one of ordinary skill in the art would not employ Rho kinase inhibitors to promote neuritogenesis of injured corneal nerves, as McKerracher fail to even mention corneal nerve injury.

Additionally, Hara teaches fasudil hydrochloride, which inhibits other protein kinases in addition to ROCK. One of ordinary skill in the art would not have been motivated to apply the specific teaching of Hara to ROCK inhibitors, in particular the other compounds recited in Applicants' claims. Further, one of ordinary skill in the art would not employ Rho kinase

inhibitors to promote neuritogenesis of injured corneal nerves, as Hara fail to even mention corneal nerve injury.

Lastly, contrary to the Examiner's assertion, one of ordinary skill in the art would not be motivated to use fasudil hydrochloride (Hara) in place of a neurotrophic factor stimulator (Hellberg) in the treatment of a corneal nerve conditions, as fasudil promotes neurite outgrowth by inhibiting the ROCK signal pathway, rather than increasing *in situ* production or activity of neurotrophic factors.

For the reasons described above, and supported by the Declaration under 37 CFR 1.132, it is clear that the subject matter of Applicants' claim 13 is patentable over the cited references, and withdrawal of the rejection is respectfully requested.

Conclusion

Therefore, in view of the foregoing remarks, it is submitted that the ground of rejection set forth by the Examiner has been overcome, and that the application is in condition for allowance. Such allowance is solicited.

If, after reviewing this Response, the Examiner feels there are any issues remaining which must be resolved before the application can be passed to issue, the Examiner is respectfully requested to contact the undersigned by telephone in order to resolve such issues.

Respectfully submitted,

Yoshiko TAKAYAMA et al.

/Amy E. Schmid/

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July 5, 2011

Attachment: Declaration under 37 CFR 1.132, with References 1-3 attached